EFFECTS OF ALPHA PARTICLES RANDOMLY INDUCED IN THE BRAIN IN THE NEUTRON-CAPTURE TREATMENT OF INTRACRANIAL NEOPLASMS

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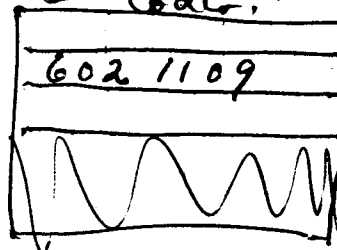Corp. Author.:

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EFFECTS OF ALPHA PARTICLES RANDOMLY INDUCED IN THE BRAIN IN THE NEUTRON-CAPTURE TREATMENT OF INTRACRANIAL NEOPLASMS

The increasing development of man's capability to explore outer space has heightened interest in the effects of primary particles, such as neutrons, protons, alpha particles and mesons, particularly when they penetrate the brain. With this problem in mind, neutron-capture therapy has been further evaluated in order to determine whether normal constituents of the brain are affected by alpha particle and energetic lithium atoms generated by the reaction used. In this procedure, the entire brain in 20 patients with intracranial tumor was exposed to thermal neutrons and to randomly generated alpha particles and energetic lithium atoms produced by the boron^{10}: thermal neutron reaction. In all 20 patients, conventional therapeutic efforts had been exhausted before neutron capture therapy was begun. Clinical data on 8 of the cases have been reported,[1] and an account of the clinical features in the remaining 12 cases together with the results of several treatment functional tests is now in progress.

In a previous article[2] our preliminary conclusions as to the effects of thermal neutrons on the brain were set forth. The present report is concerned with the results of a cytological study of parts of the brain most heavily exposed during the neutron-capture procedure. Observations of the Boron^{10}: thermal-neutron procedure on the neoplasm are being reported elsewhere.[3]

PROCEDURES

Neutron-capture therapy is a procedure by which, under certain

conditions in experimental animals, cytocidal effects can be produced through an interaction of thermal neutrons with a suitable target atom, in this case Boron^{10}, which has a thermal-neutron cross-section capture of 3840 barns. Naturally occurring Boron is composed of about 80% Boron^{11} and 20% Boron^{10}. To make the inorganic salts which we employed, an enriched Boron^{10} composed of over 96% Boron^{10} and less than 4% Boron^{11} was used. This was obtained from the Atomic Energy Commission, Oak Ridge, Tennessee. Boron^{11} does not readily interact with thermal neutrons because it has a very small capture cross section - 4.5 millibarns - and the action results in no particulate emission, only in a gamma-ray emission.

The effectiveness of neutron-capture therapy, as shown in experimentation in several animal species, depends in principle upon prompt release of a large quantity of energy within a volume equal to that of a single cell. This energy release results from abrupt Boron^{10} disintegration into an alpha particle and an energetic Lithium^{7} atom following capture of a thermal neutron by the Boron^{10} nucleus. In tissue, the combined pathway of the alpha particle and the energetic lithium atom is estimated to be about 10 microns, which, for neurons, we have taken to be of the order of one-half to one cell diameter. Under our operating conditions the energy of a thermal neutron is, by definition, 0.125 electron volts, while the Boron^{10} transformation into an energetic Lithium^{7} atom and an alpha particle results in a release of 2.345 MeV of energy.[4] When this energy value is used, the measurable, but not tissue significant, gamma contribution, which is produced in 93% of the events, is not included. For total energy release, the gamma contribution must be calculated separately

and added. The total energy absorbed from this reaction can be calculated

on the basis of neutron flux, density, length of exposure time and the

Boron concentration in the tissue. The short pathway in tissue limits the

effects of the reaction essentially to the cell in which a reaction

originates. Consequently, and in contrast with gamma effects, histological

appraisal is of great value when the site of the reaction is verified and

when specific cells are observed for the sequelae of the reaction. The

fact that the termal-neutron cloud passes through the entire brain but

at markedly differing intensities both at depth and laterally, provides

internal control checks for effects that may be observed.

After intravenous injection of an inorganic Boron salt (we have used

sodium tetraborate and sodium pentaborate) the target atom Boron^{10} is

disseminated rapidly by the circulatory system to all cell species. This

occurs prior to thermal-neutron exposure. The Boron^{10} sodium salts used

do not have a predilection for any given tissue but at hypothetical

equilibrium* would exhibit uniform concentration in body water. The rate

at which this hypothetical equilibrium may be attained varies for different

tissues, but it is quite rapid, a matter of a very few minutes at most.

Under conditions of thermal-neutron exposure in the study reported herein,

the concentration of Boron^{10} in the various types of normal cells was,

within a few minutes, sufficient to permit generation of, what experience

has shown to be, a significant number of alpha particles during the sub-

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*Hypothetical "equilibrium" because, due to significant renal excretion, a

steady state system cannot occur with a single dose.

sequent transit of the thermal neutron cloud. As compared with normal constituents of tissue (0.352 barns for H, 1.75 barns for N for the (n,p) reaction), the very high thermal-neutron cross-section capture area of Boron^{10} (3840 barns) results in approximately 90% of the released energy of all capture reactions being derived from the Boron^{10} reaction when Boron^{10} has a concentration of only 20 milligrams per kilogram of body weight. None of the tissue component reactions results in alpha particle generation, although nitrogen releases a proton with 0.624 MeV energy following thermal neutron capture. Nitrogen also has an n, gamma reaction, emitting a gamma ray of 10.8 MeV energy. For this gamma, the absorbed dose emission will be of no significance in the present context. The total gamma radiation accruing from all activation is almost entirely of very high energy and therefore does not result in a significant contribution to the absorbed dose in the general volume within the skull cavity.

In the 20 patients with whom we are dealing, use was made of two boron compounds, tetraborate and sodium pentaborate, which exhibited no difference in their response to neutrons. The differences between the two compounds appear to be limited to pharmacological properties, pentaborate being the less toxic. The inorganic salt in an aqueous glucose solution was given 6 to 30 minutes prior to the time of thermal-neutron exposure of the head. The intensity of neutron exposure is indicated by NVT per cm^2 in Table 1. Experimentation on animals has revealed no variation in brain response to neutron-Boron^{10} reactions at interval durations equivalent to those used in these patients. Therefore, within the time limits used in this study there is a seeming insensitivity to flux variations. The longest

Table 1

exposure was 40 minutes, and the shortest, 208 seconds.

Survival period of the patients varied considerably (Table 1). At autopsy, the entire brain was removed and care taken that geometrical relationships extant during life were preserved. Geometry is of extreme importance in this study because of the great dependence of thermal neutron distribution patterns on geometry. This is largely due to the very considerable attenuation of the cloud of thermal neutrons as it passes through tissue (Fig. 1). The axis of travel of the cloud must be reasonably well known in order accurately to identify regions of maximum effect.

On removal, the brains were fixed in 10% neutral formalin. Small blocks were removed from some of the brains, and were embedded in paraffin, and sections stained by various methods. The whole brain - or in those instances in which blocks were removed, the remainder of the brain - was embedded in celloidin. Whole brain sections were cut at 25 microns thickness in the coronal, horizontal or sagittal plane, then stained and mounted on slides for low-power survey. In addition, representative sections were cut at 7 microns thickness and mounted with thin cover slips for detailed microscopic examination. The following stains were utilized: hematoxylin and eosin, Bielchowsky-Plein cresyl echt violet, Loyez alum iron, Weigert's hematoxylin, and Bielchowsky-Gross silver nitrate.

Histological observations were assessed in the light of total neutron exposure, the patients position at the time of exposure, and the Boron[10] dose administered.

DOSIMETRY

The very difficult problem of dosimetry presented by this reaction system has been discussed at some length elsewhere.[5,6] From data obtained in the course of developing neutron-capture therapy at Brookhaven National Laboratory the neutron isoexposure contour pattern shown in Figure 1 was constructed and has been used in our calculations. Our basic observation measurements are presented in Table 1. In each patient, local measurements were made with gold foils and gold wires, which were activated by thermal neutrons in proportion to their number. Thus, gold wires could be used as detectors to give information on the total surface exposure to thermal neutrons and the axis of travel of the cloud of thermal neutrons and its attenuation in passing through given tissue structures. In an effort to get a better integrated dose measure, a more general procedure of measuring thermal-neutron-capture-induced gamma radiation in the exposed region was used in two patients by in vivo counting. This was not a substitute for foils but was utilized in addition to the foils.

Tissue equivalent phantoms have been used freely in order to gain better insight into many of the important factors concerned in dosimetry. Before, during and after these exposures, numerous measurements, utilizing simulated treatment geometries, were made of the gamma-ray to thermal-neutron-exposure ratio at each of the reactors under operating conditions. In both reactors under operating conditions the gamma exposure was small in relation to other exposures resulting from thermal-neutron reactions. In general it was less than 100 r and more than 50 r.

Fig. 1

D. D. Levine of the Applied Mathematics Division of Brookhaven

National Laboratory calculated the isodose contours derived from neutron

capture by tissue components, as shown in Figure 2. In this calculation

the neutron flux is represented as an exponential function of the distance

from a virtual point source 3 to 4 centimeters behind the port and integrated

by use of series expansion. The procedure yields a polynominal series

which can be used for dose calculations of induced radiation of tissue

components. For the rad dose delivered by the alpha particles and the

energetic lithium particles derived from disintegration of Boron[10] after

neutron capture the usual formula may be used for calculation:

Dose in rads = NVT x atoms per gram x σ x E x 1.6 x 10^8 gram rad MeV,

where σ is the capture cross section for Boron and E is the energy

of the reaction corrected for the fraction which is absorbed. In

case of the particles discussed herein all of the energy is

absorbed.

This formula reduces to a simpler form in which 8.67 rads are liberated

for a Boron[10] concentration of one microgram per gram of tissue and a

thermal neutron NVT of 10^{12} per square centimeter. In context of rads per

boron atom disintegration the value reduces to 37.3 x 10^{-8} rads. However,

the cytological significance of the calculated rad result is not entirely

clear because the rad unit was not derived for this type of system. We

present data thus calculated without assigning significance to the numbers,

for in the case of alpha particles randomly generated, with pathways

approximately a cell radius or a cell diameter, we have observed wide

disparities in observed tissue effects as compared with those predicted

from the above formulation or those calculated on the basis used by
Kruger.[7] This has led us to be cautious in the expression of dosage
units. In the present report, values for each term in the above equation
are provided under conditions of actual measurement. The dosage can be
calculated by the reader, and, if he desires, he can use his own formulation.
Since the purpose of this paper can well be served by relative intensity
comparisons, this method of expressing dosage units has been adopted,
although a maximum probable liklihood effect concept has been utilized
for examplar purposes. When the mechanism of energy transfer of reactions
between heavy particle and cell components at the region of maximum energy
release is more fully understood, we shall be able to draw sounder com-
parisons of proton, alpha and energetic heavy particle effects.

Under conditions of our studies in experimental animals, a rad
index of 130, which could mean a rad dosage no greater than 130, has
been found under very specific conditions to be capable of provoking a
uniform cytocidal reaction in our test neoplasms and in skin in experi-
mental animals and man. With the same NVT and boron concentration and
under these same conditions, this value would correspond to an alpha
particle dosage index of 15. This means that 15 Boron[10] disintegrations
would occur per cell. With this index, cytocidal effects can be provoked
uniformly, as indicated in the foregoing, when other conditions are fulfilled. The cytocidal
effect in experimental animals alluded to has been observed not only
in skin but also in cornea, conjunctiva, liver, kidney and in transplantable
neoplasms of mice and spontaneous osteogenic sarcoma in dogs. No changes
were seen in blood vessels in these tissues or in muscle cells or in com-
ponents of the brain.

The marked discrepancy between our observed minimum cytocidal effect following a rad dose calculated to be of the order of 130 rads and that for the production of cytological damage by alpha particles delivered by a cyclotron to the intact animal - amounting to at least 3,000 rads - is noted, but no explanation will be attempted in this report. Our rad or alpha particle index appears to be meaningful quantitatively only under the conditions described.

RESULTS

In virtually all the patients, a bone flap had been turned, and biopsy taken from the tumor region in order to establish diagnosis. A variety of pathological changes had occurred in the meninges and brain substance in the region of the biopsy or lobectomy site. In occasional cases, local infection had intervened and had been controlled through the use of antibiotics. The infective process had added to the pathological changes that had been incurred. In 2 cases (Cases 7 and 19), in which a sizeable fascial transplant had been placed over the meninges in the region in which a bone flap had been turned, a large wedge of tissue extending down to the region of the globus pallidus was massively necrotic. The necrosis was regarded as due to circulatory deficit brought about in some unknown manner by the transplant. Since the many pathological changes observed were no different from those observed in the average run of the control brain-tumor cases following brain decompression, they could not be attributed to the neutron-capture procedure.

In order to determine whether the neutron-capture-induced alpha

particle radiation had had any effect on normal brain elements, we sought out, from the serial sections, areas of the cortex which were apparently unaffected by the operative procedure but which had been exposed to the full intensity of thermal neutron exposure. Such sites were found in most of the brains. Especial attention was given those cases in which calculated rad dosage to the brain was highest (Cases 1-6).

Realizing that nerve cells can vanish without inducing any local glial response, we checked sections with the naked eye and under low magnification in an effort to determine whether cortical atrophy had occurred. No such atrophy was observed when comparison was made with corresponding cortical areas on the opposite, non-irradiated, side of the brain. The cortex in some of the brains, as that in Case 11, did show slight astroglial activation in the molecular layer and some reduction in the number of nerve cells, but since the reduction was generalized throughout the entire width of the cortex, and did not conform to isoflux areas, it was attributed to some complicating factor, not to the alpha-particle radiation. In the cortex of other brains the cortical laminae appeared to be fully populated with nerve cells. Here and there in some of the brains, foci of activated astroglia were present in relatively intact cortex. These foci were no different than those commonly observed in edematous cortex.

In short, no evidence could be found, in 18 of the 20 cases, of nerve cell damage or loss that could be attributed to the neutron-capture reaction.

One of the remaining cases (Case 1) might be an exception to the rule. In this case the brain had been exposed to the highest rad dose.

The left fronto-temporal region had been exposed to the neutrons. Brain

fungus subsequently occurred in the region of brain decompression. On

examination of brain sections, meningeal round-cell sarcoma was found to

be widespread. It formed a relatively thick layer of tumor tissue along

the convex surface of the cerebrum and in the region of the cerebellum,

but was thickest at the base of frontal lobes at the level of the optic

chiasm. Exceedingly scanty tumor was, however, present in the irradiated

area as compared with that present on the opposite side of the brain.

Presumably, much of the tumor present in this region has been destroyed

in the course of the neutron-capture therapy. Underlying brain tissue

was grossly necrotic in an area corresponding with the outer isoflux zone,

but because of the occurrence of the fungus, no conclusion could be

reached as to whether the radiation had contributed to the development

of the necrosis.

The final case (Case 2), of cerebellar sarcoma which was, for the

most part, eradicated in the neutron-capture irradiation, has been reported

on in detail elsewhere.[8, 9, 10] The cerebellar tissue was severely

damaged, but any one or more of several factors besides the neutron-capture

irradiation, such as pressure exerted by the neoplasm (which was massive)

and prior X-irradiation, could have been responsible. Four neutron-capture

treatments had been given, with striking clinical improvement after the

first two, and less improvement after the other two.

DISCUSSION

When the first of the 20 patients was given neutron-capture therapy,

we had not as yet obtained conclusive evidence that the procedure could

be cytocid/ally effective in man. Nor were we certain of the dose of
Boron salts that would be optimal, nor the total neutron exposure required.
From extensive studies in experimental animals it was, however, ascertained
that the animals had usually shown the same requirements for neutron
exposure and boron dosage for cytocidal effects as man when allowances
were made for marked differences in geometry.

The 20 patients in the present series, when evaluated in this
light, constitutes a group in which exposure was usually well in excess
of that required for the production of cytocidal effects in tumor of
mice and in skin and scalp of man (radiation dermatitis of the scalp
occurred in 7 of the patients in the present series), and skin of pigs,
dogs and rabbits, Because of the marked lateral attenuation of neutron
intensity as well as distal diminution, each observation could be doubly
controlled. Available to us as an aid in our interpretations was an
extensive study of 50 patients in which, for comparison purposes, an
effort was made to determine the effects of neoplasm growth and therapy
and the combination of surgery, X-ray and neoplasm upon normal structures
of the brain in order that the contributions of each of these several
factors might be identified with specific cytological alterations. In
the same fashion, we have utilized information in extensive animal studies
as background in estimating the cytological distribution of the Boron[10]
salts in normal brain structures. While, because of paucity of data,
we cannot in every instance in this series of patients establish exact
Boron[10] concentration, the high conformity seen between data in animals
and in man as well as well as from animal to animal and patient to patient

gives assurance that dosage calculation based upon the estimations of tissue concentrations have validity. It should be noted here that one of the original assumptions made for neutron-capture therapy was that tumors have the capacity to "seek" target elements and that both efficiency and safety of the therapy are dependent upon a high tumor: normal brain tissue ratio. Many hundreds of observations in animals have shown this assumption to be erroneous both in regard to behavior of the inorganic boron salts used and in regard to the necessity that a high ratio be obtained in order that therapy be safe and effective. Our observations indicated that the brain tissue: tumor ratio of boron salt concentration usually approximated a value of one to two. These data are presently being assembled for publication, at which time a radically different assumption for the mechanism of the reaction between Boron^{10}, thermal neutrons and cells can be expected. The details are not germane to the observations interpreted for this report.

On the other hand, we are vitally concerned with the transfer of boron from blood to normal brain tissue. Data obtained upon several of our patients from whom biopsy material was available, indicate that at the time of exposure of these patients the concentration in the normal tissue of the brain averaged, over the exposure period, a value approximately equal to the dose given in mg per kilo. It is upon this value that the exposure calculations in Table 1 are based. Observations (as yet un-published) made with chromium-labelled blood have conclusively demonstrated that to account for over 90% of analyzed tissue boron an intracellular distribution is demanded. Of the tissues studied, i.e., brain, liver,

muscle/ and tumor, only in muscle was a larger extra cellular component
found.

The data herein reported indicate that in these patients, within
the limits of the dosage administered, an exposure to randomly generated
alpha particles resulting from Boron[10] : thermal neutron capture did not,
except possibly in Cases 1 and 2, result in any perceptible alteration
in nerve cells or in other cells. Nor were any alterations observed in
the capillary bed sustaining the brain parenchyma.

The rad index provided in this paper suggests that the radiation
exposure is low when comparison is made with alpha particle beam ex-
posures of the brain from external sources. Using a cyclotron, Malis,
Loevinger, Kruger and Rose[11] were able to obtain a discrete lesion in
the cerebral cortex of cats with a radiation dose estimated to be about
5000 rads at the peak of the Bragg curve. In using alpha particle beams,
Lawrence, Tobias, Born, Wang and Linfott[12] reported that a dose of
2500 rads was effective in reducing the size of a malignant tumor. Usually
they gave a larger dose ranging from 5,000 to 8,000 rads. When other
high-energy particles, such as deuterons or protons were used, a minimal
dose of 5,000 rads was required to obtain an effect. For pituitary
extirpation, single doses of 30,000 rads were necessary. Zeman, Curtis,
Gebhard and Haymaker,[13] using a 25 μ beam of protons, concluded that the
nerve cells and glia cells suffered morphological changes before vascular
damage was evident. Jansen, Klatzo, Miquel, Brustad, Behar, Lyman,
Tobias and Haymaker[14] carried out a time-dose study on the brains of
rats through the use of alpha particles (12 MeV per nucleon and a brain

surface dose of 6,000 rads, corresponding to an estimated Bragg-peak
dose of 30,000 rad). The minimal peak dose at which nerve-cell damage
was observed was 7,500 rad, and then only after a latent period of 7
months. At higher peak doses, nerve cell and glial damage shortly pre-
ceded vascular permeability changes. Estable-Puig, Tobias and Haymaker,[15]
studied similarly irradiated brains of rats, and observed that myelin was
highly radiovulnerable. Lippincott, Calvo, Baker, Jesseph, Jansen and
Farr[16] found some increase in the number of giant cells in tumor trans-
plants exposed to a beam of 20 MeV deuterons at doses of 2,500 rads and
up to 10,000 rads, but not at 2,000 rads or less. Barendsen, Walter,
Fowler and Bewley[17] have reported high death rates in human kidney cells
in tissue culture given single exposures to approximately 244 rads with
cyclotron-generated alpha particles having an energy of 8.3 MeV. This
value, it should be noted, is compatible with the rad dose exposure
in our patients. At this dosage, we have found, cell death occurs in
tumors irradiated by our system of alpha-particle generation. A very
recent review of biological effects of particle radiation will be found
in the paper of Lippincott et al.[18] With an 11-microcurie dose of
Astatine[211] delivering an alpha particle dose of 35,000 rad to the thyroid
gland, Lippincott, Shellaburger and Basson[19] demonstrated that the gland
was almost completely annihilated. They did not employ smaller doses.
Using as a measure the accumulation of iodine by the thyroid gland,
Basson and Shellaburger[20] found the alpha particle of Astatine[211] to have
an RBE of 2.8.

From the summation of experiences it is clear that alpha particle

doses of thousands of rads may be required to produce cellular changes when the radiation comes from an external source. However, in the tissue culture study already alluded to, Barendsen et al.[17] showed that exposure to low hundreds of rads may have definite cytocidal effects. This is in agreement with our result in experimental animals. However, no cytological damage attributable to alpha-particle radiation was observed in 18 of the 20 human brains. These data strongly indicate that, under the conditions described, randomly generated alpha particles in number sufficient to provoke cytocidal effects in skin and in tumors produced no evident changes in nerve cells or in supporting elements. Whether in the other 2 cases, alpha-particle radiation did, actually, destroy normal cells cannot be said. In one (Case 1) there were 92 disintegrations per cell, with the total dose of 4×10^{-5} rads per cell (37×10^{-8} rads per disintegration), and in the other case (Case 2) the accumulated dose per cell was much higher.

<div align="center">SUMMARY</div>

Data are presented in a study of 20 patients subjected to neutron-capture therapy for intracranial neoplasm. Within the limits of exposure used, no effect was observed in nerve cells, glial cells or in vessels that could be attributed to the interaction of thermal neutrons and Boron[10] under conditions capable, in these patients, of generating a marked cytocidal effect in both tumor and skin. Two possible exceptions to this rule are cited in the text.

The data strongly suggest that nerve cells and supporting structures have a considerable tolerance for randomly generated alpha particles. A

higher exposure than we attained appears to be requisite to elicit
cytological changes, but this conclusion requires additional patient
observation and animal studies for further documentation.

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LEGENDS

Fig. 1. Attenuation of thermal-neutron cloud in passing through cranial and intracranial tissues. The curves are derived from data obtained in study of patients given neutron-capture therapy.

Fig. 2. (Legend is on the figure.)

Fig. 1

NEUTRON ISO-FLUX
CONTOURS IN n/cm²

1 %
2 %
5 %
10 %
20 %
50 %
100 %

10cm

4 cm

REACTOR BEAM
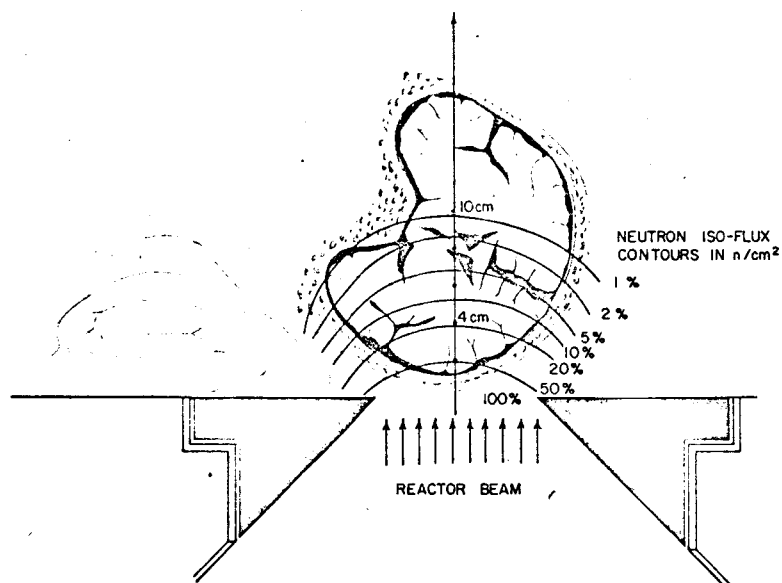
RADIATION ISO-DOSE CURVES
FROM (n γ) AND (n p) REACTIONS
WITH NORMAL TISSUE CONSTITUENTS
8 × 8 cm FIELD

100%   A

90%

80%

70% — 2 cm

60%

50%

(NOT CALCULATED)   40% — 4   (NOT CALCULATED)

30%

20% — 6

10% — 8

— 10

5%
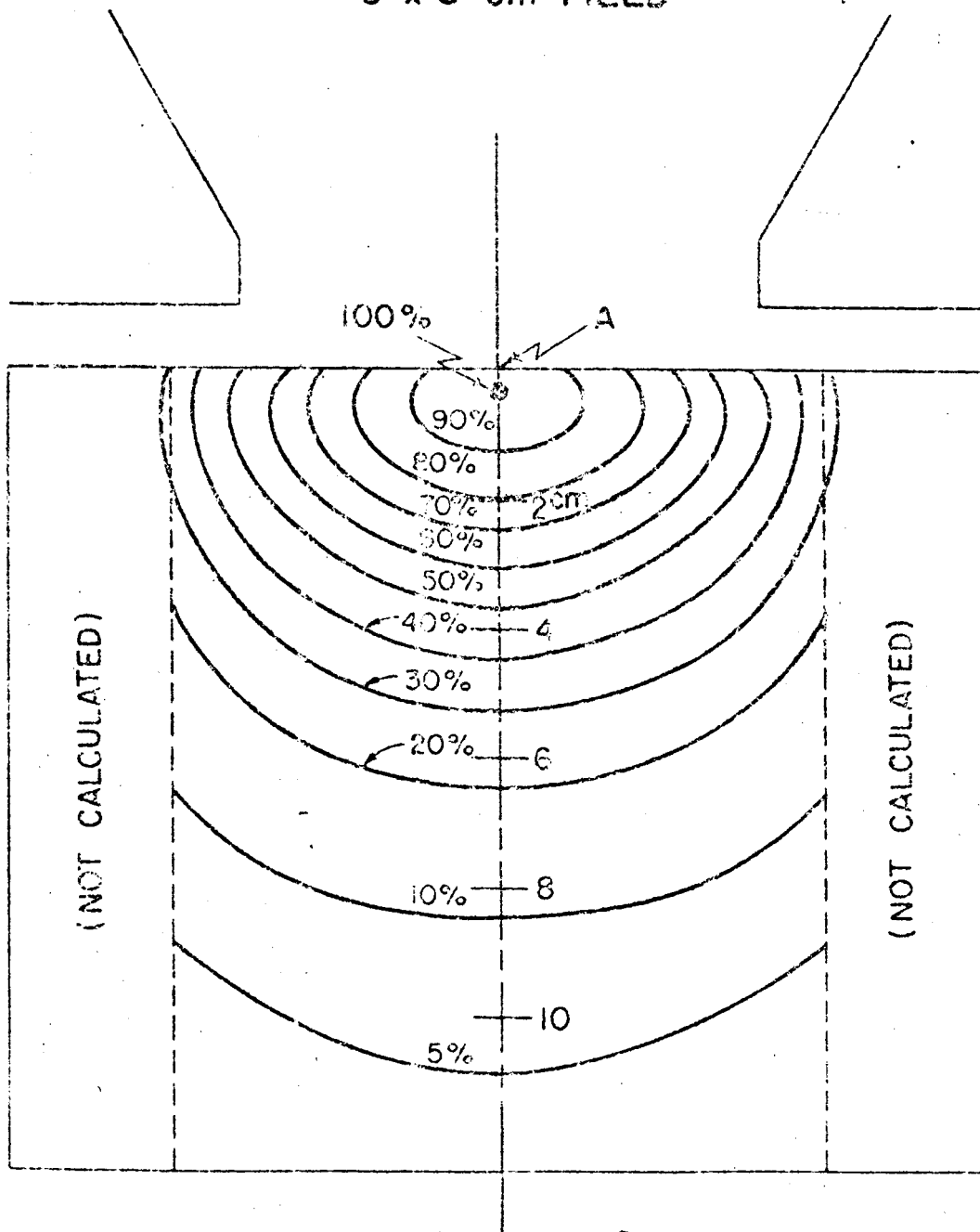
100% = 600 rad FOR nvt = 10^{13} n/cm^2 AT A

TABLE 1

Clinical, Physical and Dosimetric Summary data on 20

Patient History No.	AGE	SEX	Tumor Type	Tumor Location	Prior Radiation	Days from Surgical Exploration to First Thermal Neutron Exposure	Boron[10] dose mg/kilo	The... NVT
DR 6408 1	31	F	Meningeal sarcoma	Left temporal	None	58	47	
LG 80028 2	11	F	Hemangio-sarcoma	Cerebellar	7900 r X-radiation	354	36 32 35 35	
SN 6629 3	30	M	Anaplastic ependymoma	Right Temporo-parietal	None	40	42	
MH 6012 4	43	F	Glioblastoma multiforme	Right temporal	None	120	41 41	
JM 6480 5	38	F	Glioblastoma multiforme	Right parieto-temporal	None	90	50	
GT 6351 6	46	F	Cerebral angiosarcoma	Right temporal	None	44	41	
MK 6546 7	50	M	Glioblastoma multiforme	Right temporo-parietal	None	42	46	
FG 80083 11	44	M	Oligodendro-glioma	Left frontal	1000 r X-radiation	150	35	
RT 5984 8	49	M	Glioblastoma multiforme	Right parieto-occipital	None	14	32 32	
ED 5972 9	37	M	Diffuse astro-cytoma	Right temporal	None	46	42	
MF 6024 10	59	F	Glioblastoma multiforme	Right occipital	None	96	34	
GF 4045 12	60	M	Glioblastoma multiforme	Right parieto-temporal	None	75	29	
AH 5144 13	33	F	Glioblastoma multiforme	Right temporo-occipital	None	123	40 40 40 40	
WL 4055 14	38	M	Glioblastoma multiforme	Left temporo-parietal	None	47	26	
AB 4653 15	58	M	Glioblastoma multiforme	Right frontal	None	48	19 19 19 16	
AR 4227 16	45	M	Glioblastoma multiforme	Right parieto-occipital	None	152	25	
TF 4737 17	52	M	Glioblastoma multiforme	Right temporo-parietal	None	75	27 27	
CB 8155 18	62	M	Glioblastoma multiforme	Right frontal	None	72	25	
PP 4709 19	53	M	Glioblastoma multiforme	Left temporal	Argon-41 locally*	88	21 21 21	
PN 3977 20	51	F	Glioblastoma multiforme	Left temporo-occipital	None	76	20	

* The Argon-41 was introduced locally twice prior to neutron exposure

NVT = total neutron exposure in plane of reference

f = fraction (2 cm 1...
f' = fraction surface

TABLE 1

etric Summary data on 20 Patients

Days from surgical exploration to First thermal neutron exposure	Boron[10] dose mg/kilo	Thermal Neutron Exposure To Presenting Surface NVT $cm^2 \times 10^{12}$	Cortex Cells at Surface Rad Index f'=0.50	Alpha Index f=0.50	Cortex Cells at 4 cm Depth Rad Index f'=0.075	Alpha Index f'=0.075	Days Survival after Thermal Neutron Exposure
58	47	3.92	799	92	120	14	94
354	36	2.35	367	42	54	6	262
	32	3.46	479	55	72	8	183
	35	2.43	369	43	55	6	101
	35	4.81	730	84	109	13	28
40	42	3.84	699	81	105	12	130
120	41	2.34	415	45	62	7	337
	41	3.79	670	72	100	11	145
90	50	2.98	646	74	97	11	147
44	41	3.21	570	66	86	10	321
42	46	2.74	546	63	82	9	137
150	35	1.74	264	30	40	5	32
14	32	3.53	490	56	73	8	173
	32	3.78	324	60	77	9	138
46	42	2.72	495	57	74	9	120
96	34	2.44	360	41	54	6	244
75	29	1.46	183	21	27	3	43
123	40	0.96	166	19	25	3	152
	40	0.91	158	18	24	3	96
	40	0.96	166	19	25	3	33
	40	0.90	156	18	23	3	5
47	26	1.42	160	18	24	3	83
48	19	1.47	121	14	18	2	186
	19	1.93	159	18	24	3	160
	19	0.93	77	9	11	1	97
	16	0.98	68	8	10	1	42
152	25	1.42	153	18	23	3	100
75	27	0.86	101	12	15	2	136
	27	0.70	82	9	12	1	56
72	25	0.85	92	10	14	2	34
88	21	0.93	85	10	13	1	97
	21	0.70	64	7	10	1	83
	21	0.72	65	8	10	1	24
76	20	0.44	38	4	6	0.7	67

f = fraction of surface neutrons reaching plane at cortical surface (2 cm level)

f' = fraction of surface neutrons reaching plane at 4 cm below cortical surface (6 cm level)